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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/673,707
Filing Date: January 11, 2001
Appellant(s): PASTAN ET AL.

Laurence J. Hyman
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4-22-2008 appealing from the Office action mailed 5-3-2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

This appeal involves claims 1-7, 9, 11, 52-55, 57, 68-75 and 77.

Claims 19-24, 59-65, 79-88, 90-97, 99 and 101-103 are withdrawn from consideration as not directed to the elected invention.

Claims 8, 10, 12-18, 25-51, 56, 66-67, 76, 78, 89, 98 and 100 have been canceled.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

GROUNDS OF REJECTION NOT ON REVIEW

The following grounds of rejection have not been withdrawn by the examiner, but they are not under review on appeal because they have not been presented for review in the appellant's brief.

The rejection of claims 1, 52, 68 and 74 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "which 3B3 Fv consists of a VH chain and a VL chain encoded by SEQ ID NO:2".

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 9, 11, 52-55, 57, 68-72, 74-75 and 77 stand rejected under 35 U.S.C. 103(a) as obvious over Matsushita et al. (Aids Research and Human Retroviruses Vol. 6 No. 2, 1990, pages 193-203) in view of Barbas et al. (PNAS Vol. 91, 1994, pages 3809-3813 – IDS-5) and Pastan et al. (U.S. Patent 5,458,878 – IDS-5).

Matsushita et al. disclose anti-gp120 immunotoxins comprising the 0.5β antibody coupled to the *Pseudomonas* exotoxin (see abstract).

Matsushita et al. differs from the instant invention in that they don't disclose the use of the 3B3 antibody or the use of altered PE40.

Barbas et al. disclose a human antibody to gp120 (3B3) with broad strain cross-reactivity (see page 3812-3813).

Pastan et al. disclose modifications of the carboxyl terminus of the PE molecule resulting in increased cytotoxicity (see abstract and column 3, line 27 to column 4, line 10).

Given that Matsushita et al. suggest the use of an antibody that is broadly reactive with a number of HIV isolates (see page 200), it would have been obvious for one of ordinary skill in the art to use the 3B3 antibody in the immunotoxin disclosed by Matsushita et al. Moreover, it would a have been equally obvious for one of ordinary skill to incorporate the PE modifications disclosed by Pastan et al. in order to take advantage of the resulting increase in cytotoxicity. It should be noted that while the incorporation of immunotoxins in kits is not explicitly disclosed

by Matsushita et al., said incorporation would have been obvious to one of ordinary skill in the art in order to reduce cost and ease preparation time. It should be noted that while the sequence of the 3B3 antibody is not explicitly disclosed, it is deemed in absence of evidence to the contrary to be the same as that of the 3B3 of the instant application (SEQ ID NO:1).

Moreover, given that the anti-gp120 immunotoxins is well known in the art yielding predictable results, it is obvious for the skilled artisan to utilize any known anti-gp120 antibody (see *KSR International Co. v. Teleflex Inc.*, No. 04-1350 [U.S. Apr. 30, 2007]).

(10) Response to Argument

A. Any Motivation created by the Matsushita immunotoxins was destroyed by the failure of anti-gp120 immunoconjugates in clinical trials.

Appellant argues:

1. By focusing on Matsushita, the rejection ignores all the information available to the person of skill in the art at the time of the invention was made including the results of two clinical trials of toxins targeted to the HIV gp120 glycoprotein.

2. Ramachandran et al. and Davey et al. disclose the failure of the CD4-PE40 and sCD4-PE40 in clinical trials.

3. Goldstein and Berger et al. disclose that the failure for the CD4-PE diminished the enthusiasm for CD-PE40 in particular and Env-targeted toxins in general.

4. The present invention stems from that fact that the inventors realized that toxins targeted to gp120 would be an effective means for killing cells that serve as HIV reservoirs in patients with

reduced viral loads due to other treatments (e.g. HAART). Hence the inventors developed the instant invention as a solution to a long felt need for additional treatment strategies.

Examiner Rebuts

With regard to Points 1-3, the Matsushita reference disclosed the efficacy of an immunotoxin comprising an anti-gp120 antibody and a PE toxin. Appellant argues that the failure of immunotoxins comprising CD4 (or sCD4) and the PE toxin would deter the skilled artisan from trying to improve the immunotoxin of Matsushita. It is the Examiner's position that the two immunotoxins are not analogous and that the success of the gp120-PE immunotoxin disclosed by Matsushita would carry more weight with the skilled artisan than the failure of a non-analogous immunotoxin. The Appellant's arguments are based on the fact that both the anti-gp120-PE and the CD4-PE immunotoxins will bind to cells expressing gp120 (i.e. HIV-1 infected cells). However, the Appellant has ignored the fact that while both immunotoxins may bind to cells expressing gp120, the CD4-PE immunotoxin would also bind to all of the natural ligands of CD4 (e.g. IL16 etc.) thereby affecting untold cellular processes and endocrine cascades. The anti-gp120-PE immunotoxin, in contrast, would only bind to cells expressing gp120 (i.e. HIV-1) infected cells. Therefore, contrary to Applicant's assertion, the gp120-PE and the CD4-PE immunotoxins are not equivalent. Moreover, the failure of the CD4 based immunotoxins in clinical trials would motivate, not discourage, the skilled artisan to improve on the gp120 based immunotoxin of Matsushita, as the skilled artisan would immediately realize that it would target only HIV-1 infected cells. This hypothesis is supported by the Appellants themselves wherein they state "The toxicity of CD4-PE40 is probably due to the CD4 portion

directing the immunotoxin to the liver…" and that gp120 based immunotoxins "should be devoid of the non-specific toxicity observed with CD4-PE40." (see right hand column of page 389 of Bera et al. Molecular Medicine, 1998, Vol. 4, pages 384-391, of record). Moreover, it should be noted that the Matsushita and Bera references predate the publication of the CD4-PE clinical trials. Consequently, said results would have not effect on the thought processes (motivations) of the skilled artisan.

With regard to Point 4, Appellants logic is not consistent. If, as argued by Appellant, the failure of the CD4 based immunotoxins in clinical trials dissuaded the skilled artisan pursuing their use as a treatment modality, they would not have been motivated to use them to target reservoir cells as they would still have the same toxicity issues. However, as discussed *supra*, the skilled artisan would have analyzed the results of the clinical trials and would have realized that the observed may have been due to the CD4-PE immunotoxin binding to CD4's natural ligands. The skilled artisan, as did the inventors of the instant application, would be motivated to develop a more rigidly targeted immunotoxin such as the anti-gp120-PE immunotoxin of Matsushita.

B. The Ramachandran and Davey Conjugates and the Immunotoxins of the Invention are Analogous.

Appellant argues:

1. The Declaration by Dr. Fitzgerald stated that the CD4-PE40 immunotoxin of Ramachandran and the CD4-PE immunotoxin of Davey were intended to bind cells infected with HIV-1 as were the immunotoxins of the instant invention.

2. Dr. Fitzgerald declared that those of skill in the art would consider the immunotoxins of the instant invention analogous, *in terms of the cells they were intended to bind*, to the immunotoxins of Ramachandran and Davey.

3. The Examiner acknowledged that CD4-PE conjugates bind to cells expressing gp120 thereby acknowledging that CD4-PE immunotoxins and anti-gp120 immunotoxins were "analogous".

4. The Examiner failed to set forth any differences that might exist between the CD4 and anti-gp120 antibodies as components that would lead persons of skill to disregard the failure of the CD4-PE immunoconjugates in favor of the *in vitro* experiments of Matsushita.

5. Dr. Fitzgerald contradicted the assertion that the demonstrated efficacy of the Matsushita immunotoxin would have a greater impact on the skilled artisan than the failure of an immunotoxin comprising different components by declaring that the *in vitro* efficacy would not by itself give the skilled artisan any reason to expect a different result with the 0.5β antibody of Matsushita than that found in clinical trials of CD4-PE toxins.

6. Dr. Fitzgerald's declaration demonstrated that the PE based toxins would not bind to healthy cells and that both the CD4-PE and the Matsushita immunotoxins would be bind the same cells thus destroying the premise that the Matsushita immunotoxins and the CD4-PE immunotoxins were not analogous.

Examiner Rebuts

With regard to Points 1 and 2, the declaration by Dr. Fitzgerald was limited solely to what cells the immunotoxins were *intended* to bind not what they actually would bind. Consequently, Appellant's statement that CD4-PE immunotoxins are analogous to anti-gp120-PE immunotoxins is misleading as CD4-PE immunotoxins will bind to other "ligands" (i.e. all

the natural ligands of CD4) whereas the anti-gp120-PE immunotoxins will only bind to cells expressing gp120.

With regard to Point 3, the Examiner's acknowledgement that CD4-PE immunotoxins bind to gp120 is not an acknowledgement that CD4-PE immunotoxins and anti-gp120-PE immunotoxins are “analogous” or "equivalent" in any way other than they both bind gp120.

With regard to Point 4, .Appellant’s arguments on the point that both the anti-gp120-PE and the CD4-PE immunotoxins will bind to cells expressing gp120 (i.e. HIV-1 infected cells). However, the Appellant has ignored the fact that while both immunotoxins may bind to cells expressing gp120, the CD4-PE immunotoxin would also bind to all of the natural ligands of CD4 (e.g. IL16 etc.) thereby affecting untold cellular processes (as evidenced by the failure of the immunotoxins of Ramachandran and Davey in clinical trials). The anti-gp120-PE immunotoxin, in contrast, would only bind to cells expressing gp120 (i.e. HIV-1) infected cells. Therefore, contrary to Applicant’s assertion, the gp120-PE and the CD4-PE immunotoxins are not analogous (equivalent) and are not only structurally but also functionally different. Moreover, the failure of the CD4 based immunotoxins in clinical trials would motivate, not discourage, the skilled artisan to improve on the gp120 based immunotoxin of Matsushita, as the skilled artisan would immediately realize that it would target only HIV-1 infected cells.

With regard to Point 5, the skilled artisan would have realized that the 0.5β antibody of Matsushita would more selectively target the infected cells as compared to the CD4 based immunotoxins (which the skilled artisan would know would necessarily bind to all the natural CD4 ligands as well as HIV infected cells). Moreover, the skilled artisan would have come to the that cytotoxicity associated with the CD4 based immunotoxins was due to the CD4 portion of the

immunotoxin (a view shared by the Appellant -- see right hand column of page 389 of Bera et al. Molecular Medicine, 1998, Vol. 4, pages 384-391, of record). Given the need for HIV treatment modalities, the skilled artisan would have been motivated to explore/develop any treatment modality that showed promise (e.g. *in vitro* efficacy etc.). Consequently, the statements of Dr. Fitzgerald are not deemed persuasive.

With regard to Point 6, while the Declaration by Dr. Fitzgerald demonstrated that the CD4-PE immunotoxins would not bind healthy cells via CD4 (which was acknowledged by the Examiner) and that both immunotoxins would bind to cells expressing gp120, said demonstration cannot be extrapolated to be a demonstration that both immunotoxins are analogous or that the CD4 and anti-gp120 components of said immunotoxins are "equivalents". While both components bind gp120, the CD4 component will bind all of its natural ligands. The fact that the anti-gp120 antibody will only bind to HIV infected cells (i.e. gp120), in itself, would motivate the skilled artisan to use it instead of CD4 in an immunotoxin.

It should be noted that while Dr. Fitzgerald is not an inventor of the instant invention, he is employed by the assignee and has coauthored numerous articles with the instant inventors. Moreover, the references cited by Appellant (i.e. Goldstein et al. and Berger et al.)were coauthored by members of the inventive entity and hence are not deemed to representative of the views of the art as a whole or even an objective third party.

C. The Final Actions Points Do Not Overcome the Showing of Lack of Motivation to Modify the Matsushita Immunotoxins.

Appellant argues:

1. The Examiner's hypothesis that the hepatotoxicity seen in the CD4-PE clinical trials is due to the disruption of some cellular cascade is unsupported speculation.

2. Even if such a cascade was indeed the cause of said hepatotoxicity, it would fail to explain why a person of skill would not expect the same effect, resulting in hepatotoxicity, with the use of the Matsushita immunotoxins.

3. The *in vitro* efficacy of the Matsushita immunotoxin is the same as that of the CD4-PE immunotoxin.

4. The *in vitro* efficacy of the Matsushita immunotoxin fails to explain why the skilled artisan would not expect the Matsushita immunotoxins to induce the same hepatotoxicity as the CD4-PE given that they bind the same cells.

5. The assertion that the demonstrated efficacy of the Matsushita immunotoxin would have a greater impact on the skilled artisan than the failure of an immunotoxin comprising different components ignores evidence that the reverse is true (see Berger et al. and Goldstein references).

6. Dr. Fitzgerald's statement that there would be no reason to think that the hepatotoxicity observed in the trials of CD4-PE immunotoxins would not be also found in respect to toxins targeted by the antibody of Matsushita is not an unsupported assertion but a logical conclusion based on the correction of scientific errors made by the Examiner.

7. The CD4-PE conjugates and the Matsushita immunotoxin were considered analogous by persons of skill. The examiner's reliance on the fact that the Matsushita immunotoxin would not have been considered analogous to the CD4-PE conjugate is based on scientific fallacy and ignores the evidence of record.

8. The Examiner dismissed the evidence that Matsushita immunotoxin had never been brought into clinical trials.

9. The fact that there are no publications on the development of anti-gp120 immunotoxins in the time between the Matsushita reference and the instant application is indication that the skilled artisan would not have been motivated by the Matsushita reference to develop an anti-gp120 immunotoxin.

Examiner Rebuts:

With regard to Points 1 and 2, Appellant's arguments are predicated on the fact that both the anti-gp120-PE and the CD4-PE immunotoxins will bind to cells expressing gp120 (i.e. HIV-1 infected cells). However, the Appellant has ignored the fact that while both immunotoxins may bind to cells expressing gp120, the CD4-PE immunotoxin would also bind to all of the natural ligands of CD4 (e.g. IL16 etc.) thereby affecting untold cellular processes (as evidenced by the failure of the immunotoxins of Ramachandran and Davey in clinical trials). The anti-gp120-PE immunotoxin, in contrast, would only bind to cells expressing gp120 (i.e. HIV-1) infected cells. Therefore, contrary to Applicant's assertion, the gp120-PE and the CD4-PE immunotoxins are not analogous (equivalent) and are not only structurally but also functionally different. Moreover, the failure of the CD4 based immunotoxins in clinical trials would motivate, not discourage, the skilled artisan to improve on the gp120 based immunotoxin of Matsushita, as the skilled artisan would immediately realize that it would target only HIV-1 infected cells.

With regard to Points 3-6, the skilled artisan would have realized that the 0.5β antibody of Matsushita would more selectively target the infected cells as compared to the CD4 based immunotoxins (which the skilled artisan would know would necessarily bind to all the natural

CD4 ligands as well as HIV infected cells). Moreover, the skilled artisan would have come to the that cytotoxicity associated with the CD4 based immunotoxins was due to the CD4 portion of the immunotoxin (a view shared by the Appellant -- see right hand column of page 389 of Bera et al. Molecular Medicine, 1998, Vol. 4, pages 384-391, of record). Given the need for HIV treatment modalities, the skilled artisan would have been motivated to explore/develop any treatment modality that showed promise (e.g. *in vitro* efficacy etc.). Consequently, the statements of Dr. Fitzgerald are not deemed persuasive. Moreover, while the Declaration by Dr. Fitzgerald demonstrated that the CD4-PE immunotoxins would not bind healthy cells via CD4 (which was acknowledged by the Examiner) and that both immunotoxins would bind to cells expressing gp120, said demonstration cannot be extrapolated to be a demonstration that both immunotoxins are analogous or that the CD4 and anti-gp120 components of said immunotoxins are "equivalents". While both components bind gp120, the CD4 component will bind all of its natural ligands. The fact that the anti-gp120 antibody will only bind to HIV infected cells (i.e. gp120), in itself, would motivate the skilled artisan to use it instead of CD4 in an immunotoxin.

With regard to Point 7, contrary to Applicant's assertion, the Examiner's position is not based on scientific fallacy and is not contrary to the evidence of record. The facts of record are as follows:

- The CD4-PE immunotoxins will bind to gp120 and all natural ligands of CD4 present in the body.
- The Matsushita immunotoxins will bind only to cells bind to gp120. Therefore, CD4-PE immunotoxins and the Matsushita immunotoxins have radically different binding specificities.

- Appellant has ignored the fact that CD4-PE immunotoxins would bind to targets other than HIV infected cells.
- gp120 is a viral protein not involved in any normal cellular processes or endocrine cascades.
- Dr. Fitzgerald declared that the immunotoxins of the instant invention analogous, to the immunotoxins of Ramachandran and Davey. *in terms of the cells they were intended to bind* (not to what they actually bind). The declaration ignores the fact that the CD4-PE immunotoxins would necessarily bind to any natural CD4 ligand present.
- The skilled artisan would properly surmise that the hepatoxicity associated with the CD4 based immunotoxins was due to the CD4 portion of the immunotoxin (a view shared by the Appellant -- see right hand column of page 389 of Bera et al. Molecular Medicine, 1998, Vol. 4, pages 384-391, of record).

There existed then as there exists today a need for AIDS treatments. This need would motivate the skilled artisan take the immunotoxin of Matsushita and modify it to overcome its shortcomings. Applicant's arguments regarding the effect of the results of the CD4-PE clinical trials is not germane as both the Matsushita and Bera references were published prior to said trial results. Consequently, said results would have not effect on the thought processes (motivations) of the skilled artisan. However, even if said results were known, the skilled artisan would have analyzed the results of the clinical trials and would have surmised that the observed toxicity may have been due to the CD4-PE immunotoxin binding to CD4's natural ligands. The skilled artisan, as did the inventors of the instant application, would be motivated to develop a more rigidly

targeted immunotoxin such as the anti-gp120-PE immunotoxin of Matsushita to overcome this shortcoming. This is a logical conclusion based on *all* the facts and evidence of record.

With regard to Point 8, the fact that the Matsushita immunotoxin has been brought to clinical trials is off-point. Whether the resulting immunotoxin would be successful in clinical trials is irrelevant, the issue is whether or not the skilled artisan would have been motivated to modify the immunotoxin of Matsushita. For the reasons set forth above, the skilled artisan would have been motivated to make such a modification.

With regard to Point 9, Appellant is reminded that Matsushita discloses an anti-gp120 immunotoxin. The motivation is to substitute the low affinity 0.5β antibody of the Matsushita immunotoxin with the 3B3 antibody of Barbas et al. and utilize the PE toxin of Pastan et al. Given that Matsushita et al. suggest the use of an antibody that is broadly reactive with a number of HIV isolates (see page 200), it would have been obvious for one of ordinary skill in the art to use the 3B3 antibody in the immunotoxin disclosed by Matsushita et al. Moreover, it would a have been equally obvious for one of ordinary skill to incorporate the PE modifications disclosed by Pastan et al. in order to take advantage of the resulting increase in cytotoxicity. Moreover, given that the anti-gp120 immunotoxins is well known in the art yielding predictable results, it is obvious for the skilled artisan to utilize any known anti-gp120 antibody (see *KSR International Co. v. Teleflex Inc.*, No. 04-1350 [U.S. Apr. 30, 2007]). Finally, the logical extension of known scientific principles need not be published to be obvious to the skilled artisan.

Finally, the Examiner has no way of evaluating the multiple factors (having nothing to do with the aforementioned scientific facts) that dictate whether of given investigator pursues a given course of research. Consequently, the lack of publications cannot be an indication of non-

obviousness. Moreover, since the Matsushita and Bera references predate the publication of the results of the CD4-PE clinical trials said results would have not effect on the thought processes (motivations) of the skilled artisan.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Primary Examiner, Art Unit 1645

Conferees:

/Shanon A. Foley/

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